

STATISTICAL ANALYSIS PLAN

Doc. Control #: CP-00019

SAP Version #: 1.0

Version Date: May 30, 2018

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Protocol Number	P500-0717
Protocol Title	The ENCORE Study: Safety Evaluation of Repeat Placement of the Corticosteroid-Releasing S8 Sinus Implant in Chronic Sinusitis Patients with Nasal Polyps
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Investigational Product	S8 Sinus Implant

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APPROVAL SIGNATURES

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REVISION HISTORY

Version	Date	Summary of Changes/Comments
1.0	30May2018	Document created

1.0 INTRODUCTION

This statistical analysis plan (SAP) outlines the data and procedures to be used for assessing the safety and efficacy endpoints in the ENCORE Study conducted by Intersect ENT under protocol P500-0717 entitled “Safety Evaluation of Repeat Placement of the Corticosteroid-Releasing S8 Sinus Implant in Chronic Sinusitis Patients with Nasal Polyps.” Preparation of this analysis plan was based on the protocol version 2.0 dated October 12, 2017. The purpose of this document is to provide further details regarding the analysis plan.

2.0 STUDY OBJECTIVE

To assess the safety of repeat placement of the S8 Sinus Implant when used in chronic sinusitis (CS) patients with recurrent nasal polyps.

3.0 STUDY DESIGN

This is a prospective, non-randomized, open-label, multicenter clinical trial enrolling up to 50 subjects at up to 10 study centers across the U.S. Eligible subjects undergo in-office bilateral placement of the S8 Sinus Implant in the ethmoid sinuses (total of two implants). Subjects return for seven follow-up visits at Days 30, 60, 90, 120, 150, 180 and 365 (see Appendix A Schedule of Assessments). All implants are removed by Day 90. Subjects meeting eligibility criteria for repeat placement undergo repeat in-office placement of the S8 Sinus Implant in each ethmoid sinus with a nasal polyp grade ≥ 1 . All repeat implants are removed by Day 180.

4.0 STUDY ENDPOINTS

4.1 Safety Evaluation

All adverse events (AE) reported by subjects between consent and the Day 365 follow-up visit (end of study) are tabulated. Each AE is evaluated by investigators in terms of seriousness, severity (i.e., mild, moderate, severe), and strength of relationship (i.e., not related, unlikely related, possibly related, related) to study drug, study device, and implant procedure. Any AE that is determined by a participating investigator to be directly related (related and possibly related) to the study drug, study device, and/or implant procedure will be categorized as implant-related.

Note: The occurrence of a diagnostic or elective surgical procedure for a pre-existing condition, unless the condition becomes more severe or increases in frequency, would not be considered implant-related.

4.2 Efficacy Endpoints

Efficacy endpoints comprise both patient-reported and endoscopic endpoints through the Day 180 follow-up visit.

Patient-reported endpoints

- Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in the nasal obstruction/congestion score (scale 0 to 3)
- Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in the Sino-Nasal Outcome Test (SNOT-22) total score (scale 0 to 110), symptom domain scores (scales 0 to 35), and individual symptom scores (scale 0 to 5)

Endoscopic endpoints

- Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in bilateral polyp grade (scale 0 to 8)
- Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in percent ethmoid sinus obstruction (scale 0% to 100%)

4.3 Other Endpoints

Implant delivery success rate

Percentage of successful deployments of the S8 Sinus Implant to the target site per total number of sinuses attempted during the baseline and repeat placement procedures.

Interventions received

Proportion of subjects who received interventions (i.e., steroids or antibiotics for ethmoid sinus obstruction or for other reasons, polypectomy, repeat endoscopic sinus surgery) through Day 365.

Responder rates: Proportion of subjects who were responders as defined by nasal obstruction/congestion and bilateral polyp grade.

Indicated for repeat endoscopic sinus surgery (RESS) based on clinical data: Proportion of subjects who are indicated for RESS based on nasal obstruction/congestion score ≥ 2 and polyp grade ≥ 2 on each side.

Implant status: Proportion of sinuses with implant status of present, absent, or removed.

5.0 ANALYSIS POPULATION

All analyses are conducted using the safety population, which is defined as all subjects and sinuses that actually received the S8 Sinus Implant in target sinuses at baseline/procedure.

6.0 GENERAL DATA DERIVATIONS

6.1 Study Day Calculation

Study Day 1 is the day of the S8 Sinus Implant placement at the baseline/procedure. Study Day is calculated relative to Study Day 1 and appears in the listings where applicable.

If the date of event is on or after the date of the S8 Sinus Implant placement at the baseline/procedure, Study Day is calculated as:

$$\text{Study Day} = \text{Date of event} - \text{Date of procedure} + 1$$

Otherwise,

$$\text{Study Day} = \text{Date of event} - \text{Date of procedure}$$

6.2 Baseline

The baseline is defined as the last observation recorded prior to the first attempt of the S8 Sinus Implant placement.

6.3 Change from Baseline Calculation

Change from baseline is calculated as:

$$\text{Change from Baseline} = \text{Follow-Up Result} - \text{Baseline Result}$$

A negative value corresponds to a decrease (improvement), whereas a positive value corresponds to an increase (worsening).

6.4 Study Visits

Subjects return for 7 follow-up visits at Days 30, 60, 90, 120, 150, 180 and 365 (end of study). Data from protocol-specified visits (i.e., as reported in the case report form or CRF) are used in the summary tables and data listings. If unscheduled visits occur during which high-dose steroids are prescribed (and after which high-dose steroids are taken by the subject), data from those visits will be used as last observations carried forward in statistical analyses (see Section 7.3 Medical or Surgical Interventions).

6.5 General Statistical Considerations

All analyses described in this plan are considered *a priori* analyses, as they have been defined prior to locking the database. All other analyses, designed subsequently to the database lock, will represent *post hoc* analyses and will be considered as exploratory. Any *post hoc* analyses will be clearly identified in the clinical study report.

6.6 General Statistical Procedures

Statistical summaries and confidence intervals (CI) are generated using SAS[®] software, version 9.4 or higher. Descriptive statistics are provided for all summarized data by displaying the mean, standard deviation (SD), median, minimum and maximum for continuous data, and the count and percentage for categorical data. Unless stated otherwise, a two-sided 95% CI is calculated when a CI is presented. A p-value < 0.05 is considered as statistically significant.

7.0 STATISTICAL ANALYSES

7.1 Demographics and Baseline Clinical Characteristics

Demographic data (i.e., age, gender, race) and baseline clinical characteristics (i.e., number of prior endoscopic sinus surgery (ESS), days since last ESS, symptoms that have been present for ≥ 12 weeks prior to baseline, history of smoking, current status of asthma and allergic rhinitis diagnosed by physician, aspirin intolerance or aspirin allergy, and allergies) will be presented. Baseline clinical characteristics including polyp grade and Nasal Obstruction/Congestion scores

will also be summarized.

7.2 Sample Size

The 50-patient sample size was selected based on clinical judgment. In the RESOLVE II study, ~90% of sinuses had polyp grades ≥ 1 at Day 90. From this data, it is expected that of the 100 sinuses undergoing implant placement at baseline, greater than 85 sinuses would undergo repeat placements at Day 90. Therefore, a sample of 50 subjects will provide safety data on up to 185 implant procedures (100 implants at baseline; 85 implants at Day 90), which is deemed to be a large enough sample to detect potential additional implant-related adverse events associated with recurrent use of the implant.

7.3 Medical or Surgical Interventions

Since high-dose steroids (e.g., oral, parenteral, injection, budesonide or other sinus steroid irrigations, rinses or drops, nebulized steroids administered nasally) or surgical intervention may confound the efficacy measures, the following method will be applied to the analyses in cases where such interventions are performed:

- If a subject initiates high-dose steroids (see Clinical Study Protocol Appendix A for a list of medications considered as high-dose steroids) or undergoes polypectomy or revision ESS for chronic sinusitis conditions attributable to the ethmoid sinus during the study, this represents treatment failure.
- For subjects with interventions for treatment failure occurring at any time point through Day 180 (regardless of receiving repeat implant placement at Day 90), the last available scores for Nasal Obstruction/Congestion, SNOT-22, and endoscopic measures prior to interventions will be carried forward to all time points through Day 180 or the last follow-up visit.

No other data imputation rules will be applied in the planned statistical analyses. All efficacy endpoints will be presented as intervention-adjusted values.

7.4 Efficacy and Other Endpoints

Continuous measures are analyzed using descriptive statistics such as means, medians, and SD. and, where appropriate, 95% CI for the mean assuming a normal distribution.

Continuous measures include:

- Nasal Obstruction/Congestion score: Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in the mean score (scale 0 to 3)
- SNOT-22 score: Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in SNOT-22 total score, domain scores, and individual symptom scores. The total score of SNOT-22 is calculated as the sum of all items, and ranges from 0 to 110 with the highest score representing worsening. The following table lists corresponding items and ranges for each symptom domain.

SNOT-22 Domains	Survey Items	Score Range
Rhinologic Symptoms	#1, #2, #3, #6, #21, #22	0–30
Extra-Nasal Rhinologic Symptoms	#4, #5, #6	0–15
Ear/Facial Symptoms	#2, #7, #8, #9, #10	0–25
Psychological Dysfunction	#14, #15, #16, #17, #18, #19, #20	0–35
Sleep Dysfunction	#11, #12, #13, #14, #15	0–25

- Bilateral Polyp Grade: Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in bilateral polyp grade (scale 0 to 8), which represents a sum of left and right sides. The bilateral polyp grade for a given patient is set as missing if the grade for one side is missing.
- Percent Ethmoid Sinus Obstruction: Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in percent ethmoid sinus obstruction (scale 0% to 100%). Percent ethmoid obstruction scores on left and right sides are averaged for each subject at each time point. The results for a given patient is set as missing if the score for one side is missing.

Categorical measures are analyzed as counts, rates, proportions and frequencies. Where it is appropriate, 95% CI (computed using the exact method) and p-values will be presented.

Categorical measures include:

- Implant delivery success rate: Proportion of successful deployments of the S8 Sinus Implant to the target site per total number of sinuses attempted including the baseline and repeat placement procedures. Implant delivery success rate at Baseline, Day 90 and Baseline & Day 90 combined will be presented.

- Interventions received: Proportion of subjects who received interventions (i.e., sinus-related medications, systemic steroid interventions, and surgical interventions) through Day 365.
- Responder rates: Proportion of subjects with clinically meaningful improvement from baseline in nasal obstruction/congestion score and/or bilateral polyp grade at each time-point (Days 30, 60, 90, 120, 150, 180) will be presented. Responders include subjects with:
 - Nasal obstruction/congestion score, ≥ 1.0 -point reduction from baseline
 - Nasal obstruction/congestion score, ≥ 2.0 -point reduction from baseline
 - Nasal obstruction/congestion score < 2.0
 - Bilateral polyp grade, ≥ 1.0 -point reduction from baseline
 - Bilateral polyp grade, ≥ 2.0 -point reduction from baseline
 - Polyp grade < 2 on each side
 - Nasal obstruction/congestion score ≥ 0.5 and bilateral polyp grade, ≥ 1.0 -point reduction
 - Nasal obstruction/congestion score ≥ 0.5 and bilateral polyp grade, ≥ 2.0 -point reduction
 - Nasal obstruction/congestion score ≥ 1.0 and bilateral polyp grade, ≥ 1.0 -point reduction
 - Nasal obstruction/congestion score ≥ 1.0 and bilateral polyp grade, ≥ 2.0 -point reduction
- Indicated for repeat endoscopic sinus surgery (RESS) based on clinical data: Proportion of subjects who are indicated for RESS based on nasal obstruction/congestion score ≥ 2 and polyp grade ≥ 2 on each side at Day 90 and at Day 180.
- Implant status: Proportion of subjects with implant status of present, absent, or removed, as assessed at each time-point (Days 30, 60, 90, 120, 150, 180).

7.5 Safety Evaluation

Adverse events

All adverse events (AE) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Where possible, and if applicable, AE will be localized to a sinus type and side.

The incidence and percentages of AE and serious adverse events (SAE) through Day 365, including treatment emergent AE (TEAE), implant-related AE and SAE, will be presented by MedDRA system organ class (SOC) and preferred term (PT). Complete patient listings of all adverse events will be provided. For each adverse event, the following will be specified:

- Start and stop dates, and event onset (study day)
- The affected side (right or left) if available
- Seriousness
- Severity
- Strength of relationship if available
- Action taken
- Outcome

In tables presenting implant-related AE, the incidences and percentages will also be presented based on two mutually exclusive periods of observation:

- from baseline to Day 90 (before repeat placement)
- from repeat placement (at Day 90) to Day 180

Concomitant medications

Prior and concomitant medications are coded to therapeutic class and PT using the World Health Organization (WHO) Drug Dictionary. All concomitant medications are listed and summarized in a table.

8.0 APPENDICES

Appendix A: Schedule of Assessments

Assessment	Screening	Baseline/Procedure	Day 30 (\pm 7 days)	Day 60 (\pm 7 days)	Day 90 (\pm 7 days)	Day 120 (\pm 7 days)	Day 150 (\pm 7 days)	Day 180 (\pm 14 days)	Day 365 (\pm 14 days)
Informed consent	X								
Medical/surgical history	X								
Endoscopic grading & recording	X	X	X	X	X	X	X	X	
Nasal Obstruction/Congestion		X	X	X	X	X	X	X	
Sino-Nasal Outcome Test (SNOT-22)		X	X	X	X	X	X	X	
In-office implant placement (bilateral)		X							
Implant removal					X			X	
In-office repeat placement (unilateral or bilateral)					X ^a				
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events reporting	X	X	X	X	X	X	X	X	X
Pregnancy test (female subjects)	X ^b	X ^b			X ^b				
Documented birth control (female subjects)		X ^c	X	X	X	X	X	X	X

Note: If screening and baseline/procedure visits occur on the same day, assessments must be recorded on the baseline visit forms.

- ^{a.} Repeat implant placement is performed at Day 90 in each ethmoid sinus with polyp grade \geq 1.
- ^{b.} Female subjects with reproductive potential are required to undergo a urine pregnancy test at screening and prior to the baseline procedure. If the screening and baseline/procedure visits occur on the same day, only one urine pregnancy test is required prior to the baseline procedure. The pregnancy test must be repeated at Day 90 prior to repeat implant placement procedure.
- ^{c.} Female subjects are required to confirm their nursing status at baseline.

Appendix B: Table Mock-Ups

Appendix C: Listing Mock-Ups